Scientific Abstract.

Glioblastoma Multiforme is a generally fatal human malignancy in which combinations of surgical resection and chemo- and radiation therapy are ineffective. Gene transfer-based therapies used in combination with more standard approaches may provide a better outcome. Our laboratories have developed a novel replication-defective herpes simplex virus (HSV) based gene vector (Nurel-C2) that is capable of expressing multiple anti-cancer genes at high levels up to 7 days in glioblastomas in the absence of other viral functions. The transgenes include the viral infected cell protein zero (ICP0) and thymidine kinase (TK) genes, and the human genes encoding the gap junction-forming connexin 43 and tumor necrosis factor alpha (TNF-α) protein. ICP0 has been shown to arrest tumor cell division and enhance vector transgene expression, TK activation of ganciclovir (GCV) kills infected tumor cells; connexin 43 enhances bystander killing of uninfected neighboring tumor cells and TNF-α provides an additive cytotoxic effect on TNF-α sensitive tumor cells, enhances killing of TNF-α resistant cells through an intracellular mechanism and improves the effects of concurrent radiosurgery. The combination multigene, ganciclovir and radio-surgical therapies maximize tumor destruction while sparing surrounding normal neurons.

NUREL-C2 will be used in a Phase-I dose escalation clinical trial to evaluate the safety of this multifaceted treatment applied to patients with recurrent, progressive glioblastoma multiforme (GBM). Two consecutive cohorts of 8-12 patients with recurrent GBM will receive stereotactic injections of NUREL-C2 into the brain tumor. Patients with large resectable tumors will be recruited in the first cohort. The vector will be injected into the tumor mass and the tumor resected 2-4 days later and evaluated for the presence of vector genomes, transgene expression and evidence of inflammation. At the completion of tumor resection the same dose of vector contained within 8 aliquots will be injected into the residual tumor margin. Following vector injections intravenous ganciclovir will be administered for 14 days. Patients with unresectable tumors (average tumor diameter < 4 cm) will be recruited in the second cohort. These patients will receive vector intratumoral injections according to the same dose escalation schedule, followed by ganciclovir treatment for 14 days and gamma knife radio-surgery within 48 hours of virus inoculation. The size and metabolic activity of all tumors will be followed by serial MRI and Positron Emission Tomography (PET) Scans, respectively. Patients will be enrolled in groups of three, with each group receiving successively larger doses (10^7, 10^8 10^9 PFU) of HSV vector. This study will be to determine the maximal tolerated dose (MTD) of vector and the nature of possible dose limiting toxicity (DLT) associated with either arm of the treatment protocol. The secondary objective is to determine and document the responses.